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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,380	11/03/2003	Eveline Catherina Anna Clasina Timmermans	2183-5581.1US	9902

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EXAMINER	
BABIC, CHRISTOPHER M	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/700,380	CLASINA TIMMERMANS ET AL.	
	Examiner	Art Unit	
	Christopher M. Babic	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,19-21,23,24,27-31 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17, 19-21, 23, 24, 27-31, and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 11/20/2006
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claim(s) 1-17, 19-21, 23, 24, 27-31, and 34 are pending. The following Office Action is in response to Applicant's response dated February 9, 2007.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on November 20, 2006 was filed after the mailing date of the Office Action on June 1, 2006. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112 - 2nd Paragraph

The rejections of claim(s) 13-30 have been withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 112 - 1st Paragraph - Scope of Enablement

The rejections of claim(s) 13-18 and 27-33 have been withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 102

The rejections of claim(s) 13, 16, 19, 27, and 27 over Tabiti have been withdrawn in view of Applicant's amendments.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claim(s) 1-3 and 8-11 remain rejected under 35 U.S.C. 102(b) as being anticipated by Tabiti et al. (EP 1 138 783 A2).

With regard to claim(s) 1, Taibiti teaches a method (pg. 11-13, for example) comprising: amplifying the nucleic acids of interest in the amplification reaction (pg. 11, example 1, for example); measuring the amount of at least two nucleic acids of interest at at least two different time points in the reaction (pg. 11, example 1, i.e. real-time PCR, for example); determining from at least two of the measurements the amplification rate of the at least two nucleic acids of interest (pg. 11,12 example 2, table 2, efficiencies Cp-CK20 and Cp-PBGD, for example);determining a ratio of the amplification rates of the at least two nucleic acids of interest (pg. 11,12 example 2, table 2, efficiencies Cp-CK20 and Cp-PBGD, i.e. the ratio is inherent to the disclosure of

both efficiencies, for example); comparing the ratio with a reference (pg. 12, example 3, assumed efficiency for CK20 and PBGC of 2, for example); and determining, from the comparison, the initial ratio of the amounts of the at least two nucleic acids of interest in the sample (pg. 12, example 3, $N(T)_0/N(R)_0$for example). Tabiti further teaches multiplex amplification/detection (pg. 8, [0044], for example).

With regard to claim(s) 2, 3, and 8, Tabiti teaches variable salt concentration that allow detectable levels of all nucleic acids of interest (Page 13, Example 4, for example).

With regard to claim(s) 9, Tabiti teaches independent nucleic acids of interest (Page 11, Example 1, for example).

With regard to claim(s) 10 and 11, Tabiti teaches RNA (Page 11, Example 1, for example) and DNA (Page 13, Example 4, for example) nucleic acids of interest.

2. Claim(s) 1-11, 13-22, 24, and 27-34 remain rejected under 35 U.S.C. 102(e) as being anticipated by Stuyver et al. (U.S. 2003/0124512 A1).

With regard to claim(s) 1, Stuyver teach a methods for determining mitochondrial toxicity by determining the ratio of mitochondrial DNA to nuclear DNA ([0171], for example). Specifically, Stuyver teaches: amplifying the nucleic acids of interest in a multiplex amplification reaction (example 11, [0312], mitochondrial and ß-actin, for example); measuring the amount of at least two nucleic acids of interest at at least two different time points in the reaction (example 11, [0312], real-time PCR, for example);

determining from at least two of the measurements the amplification rates of the at least two nucleic acids of interest (example 11, [0313], for example); determining a ratio of the amplification rates of the at least two nucleic acids of interest (example 11, [0313], i.e. the ratio is inherent to the disclosure of both efficiencies; fig. 3, showing efficiencies are approx. equal, for example); comparing the rates with a reference (example 11, [0313]; fig. 3, comparing to dilution of target DNA, for example); and determining, from the comparison, the initial ratio of the amounts of the at least two nucleic acids of interest in the sample (example 11, [0313]; fig. 3, dilution of target DNA, for example).

With regard to claim(s) 2-8, Stuyver expressly teaches optimization of real-time RT-PCR including varying primer concentrations and salt concentrations (pg. 19,20, example 5, for example).

With regard to claim(s) 9, Stuyver expressly teaches independent nucleic acids of interest example 11, [0312], mitochondrial and ß-actin, for example).

With regard to claim(s) 10 and 11, Stuyver expressly teaches RNA and DNA nucleic acids of interest (example 11, [0312], mitochondrial and ß-actin, for example).

With regard to claim(s) 13, 16, 19, 27, 29, Stuyver teaches methods for determining mitochondrial toxicity of chemotherapeutic agents by determining the ratio of mitochondrial DNA to nuclear DNA ([0171], for example).

With regard to claim(s) 14, Stuyver expressly teaches endosymbiont cellular organelle nucleic acid (pg. 13, [0190], for example).

With regard to claim(s) 15, Stuyver expressly teaches determining the ratio of the amount of endosymbiont cellular organelle nucleic acid in relation to the amount of nuclear nucleic acid (example 11, [0312], mitochondrial and ß-actin, for example).

With regard to claim(s) 17, Stuyver expressly teaches HIV (pg. 13, [0196]-[0197], for example).

With regard to claim(s) 18, Stuyver expressly teaches RNA and DNA nucleic acids of interest (example 11, [0312], mitochondrial and ß-actin, for example).

With regard to claim(s) 20, Stuyver expressly teaches HIV (pg. 13, [0196]-[0197], for example).

With regard to claim(s) 21, 22, and 24, Stuyver expressly teaches nucleotide analogues and AZT (pg. 25, example 14, for example).

With regard to claim(s) 28, 30, and 31, Stuyver expressly teaches toxicity assays (pg. 25, example 14, for example).

With regard to claim(s) 32 and 33, Stuyver expressly teaches determining the ratio of the amount of endosymbiont cellular organelle nucleic acid in relation to the amount of nuclear nucleic acid (example 11, [0312], mitochondrial and ß-actin, for example).

With regard to claim(s) 34, Stuyver expressly teaches peripheral blood mononuclear cells ([0301], for example).

Response to Arguments - Claim Rejections - 35 USC § 102

Applicant's arguments with respect to the previously applied references have been fully considered but they are not persuasive.

Rejection of claim(s) 1-3 and 8-11, 13 over Tabiti

Applicant argues that the amended claims are novel over Tabiti because the reference does not disclose a method that determined the ratio of the amplification rates of at least two nucleic acids. Applicant further points out that the ratio of the amplification rates is correlated to the ratio of the initial amounts of the at least two nucleic acids. These arguments are not persuasive because, first, the "determining" and "comparing" steps of the claimed invention are considered "mental" or "mathematical" steps that produce values that are inherent to the disclosure of the "equation" variables. In other words, as noted in the above rejection, the ratio of the amplification rates is taught by the reference because both amplification efficiencies are disclosed. In fact, Tabiti makes note of the fact that the amplification efficiencies of CK20 and PBGD differ significantly from one another (table 2, for example). Also, the actual "correlation" of the ratio of the amplification rates of the at least two nucleic acids **to** the ratio of the initial amounts of the at least two nucleic acids is not required within the claimed invention.

Rejection of claim(s) 1-11, 13-22, 24, and 27-34 over Stuyver

The above arguments apply to the teachings of Stuyver as well.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claim(s) 4-7 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tabiti et al. (EP 1 138 783 A2) in view of Henegariu et al. ("Multiplex PCR: Critical Parameters and Step-by-step Protocol" BioTechniques. September 1997. 23: Pages 504-511).

With regard to claim(s) 4-7, the methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach varying primer concentration.

Henegariu provides a supporting disclosure that teaches optimization of multiplex reaction components such as primer concentration or primers directed to different loci (Page 508, fig. 3c, for example). They further teach overcoming uneven amplification by changing the proportions of various primers in the reactions, with an increase in the amount of primers for the "weak" loci and a decrease in the amount for the "strong" loci (pg. 508, col. 1, amount of primer, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate to optimize the primer concentrations of the multiplex reaction of Tabiti since Henegariu suggests such a modification to correct for uneven amplification.

2. Claim(s) 12 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Tabiti et al. (EP 1 138 783 A2) in view of van Deursen et al. ("A novel quantitative multiplex NASBA method: application to measuring tissue factor and CD14 mRNA levels in human monocytes" Nucleic Acids Res. 1999 Sep 1;27(17):e15).

With regard to claim(s) 12, the methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not

expressly teach multiplex quantitative nucleic acid sequence based amplification (NASBA).

van Deursen provides a supporting disclosure that teaches quantification of RNA levels in a multiplex setting (pg. ii, NASBA, for example). They further teach that since the NASBA reaction is isothermal, specific amplification of single-stranded RNA in the presence of double-stranded DNA is possible (pg. ii, NASBA, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate to quantitative multiplex NABSA reaction of van Deursen into the methods of Tabiti since van Deursen suggests such a modification to correct for amplification of single-stranded RNA in the presence of double-stranded DNA.

3. Claim(s) 12 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Stuyver et al. (U.S. 2003/0124512 A1) in view of van Deursen et al. ("A novel quantitative multiplex NASBA method: application to measuring tissue factor and CD14 mRNA levels in human monocytes" Nucleic Acids Res. 1999 Sep 1;27(17):e15).

With regard to claim(s) 12, the methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach multiplex quantitative nucleic acid sequence based amplification (NASBA).

van Deursen provides a supporting disclosure that teaches quantification of RNA levels in a multiplex setting (pg. ii, NASBA, for example). They further teach that since

the NASBA reaction is isothermal, specific amplification of single-stranded RNA in the presence of double-stranded DNA is possible (pg. ii, NASBA, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate to quantitative multiplex NABSA reaction of van Deursen into the methods of Stuyver since van Deursen suggests such a modification to correct for amplification of single-stranded RNA in the presence of double-stranded DNA.

4. Claim(s) 23 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Stuyver et al. (U.S. 2003/0124512 A1) in view of Krynetskaia et al. ("Deoxythioguanosine triphosphate impairs HIV replication: a new mechanism for an old drug" FASEB J. 2001 Sep;15(11):1902-8).

With regard to claim(s) 23, the methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach determining the therapeutic activity of the compounds set forth in claim(s) 23.

Krynetskaia provides a supporting disclosure that teaches an assay determining the anti-HIV activity of thioguanine (pg. 1904, col. 1, for example). They further teach that thiopurines represent a new class of agents with anti-retroviral activity (pg. 1907, col. 2, for example).

It would have been *prima facie obvious* to a practitioner of ordinary skill in the art to incorporate to thioguanine into the methods of Stuyver since Krynetskaia suggests such a modification to test its anti-retroviral activity.

Double Patenting

Applicant's arguments, see pg. 9 and 10, have been fully considered and are persuasive. The rejections over van Gemen et al. (U.S. 6,967,016 B2) have been withdrawn.

Conclusion

Claim(s) 1-17, 19-21, 23, 24, 27-31, and 34 are rejected. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

5/14/07

Christopher M. Babic
Patent Examiner

AU 1637

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

5/14/07